Magnesium and CVS calcification in CKD

By

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PHYSIOLOGY

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MAGNESIUM IN MAN: IMPLICATIONS FOR HEALTH AND DISEASE

plays an important role in the physiological function of the brain, heart, and skeletal muscles. Mg^{2+} has anti-inflammatory properties and acts as Ca^{2+} antagonist. The United States Food and Nutrition Board recommends a daily intake of 420 mg for men and 320 mg for women (1). However, recent reports estimate that at least 60% of Americans do not consume the recommended daily amount of Mg^{2+} (281). Part of the problem stems from the soil used for agriculture, which is becoming increasingly deficient in essential minerals. Over the last 60 years the Mg^{2+} content in fruit and vegetables decreased by 20–30% (570). Moreover, the Western diet contains more refined grains and processed food. Estimates are that 80–90% of Mg^{2+} is lost during food processing. As a result, a significant number of people are Mg^{2+} deficient, which may comprise up to 60%

The first use of Mg^{2+} in human medicine can be traced back to 1697 when Dr. Nehemiah Grew identified magnesium sulfate ($MgSO_4$) as the major ingredient of Epsom salt (195). Epsom salt was extracted from a well in Epsom, England and was used over the years to treat abdominal pain, constipation, sprains, muscle strains, hyaline membrane disease, and cerebral edema. Subsequently, Mg^{2+} was recognized as an element (Mg) by Joseph Black in 1755 and first isolated by Sir Humphrey Davy from magnesia [$Mg_3SO_4O_{10}(OH)_2$] and mercury in 1808 (102). The role of Mg^{2+} in the human body emerged once Mg^{2+} was described in blood plasma by Willey Glover Denis in 1920 (113). In 1926, Jehan Leroy demonstrated that Mg^{2+} is essential for life in mice (309). These findings were trans-

Blood Purification
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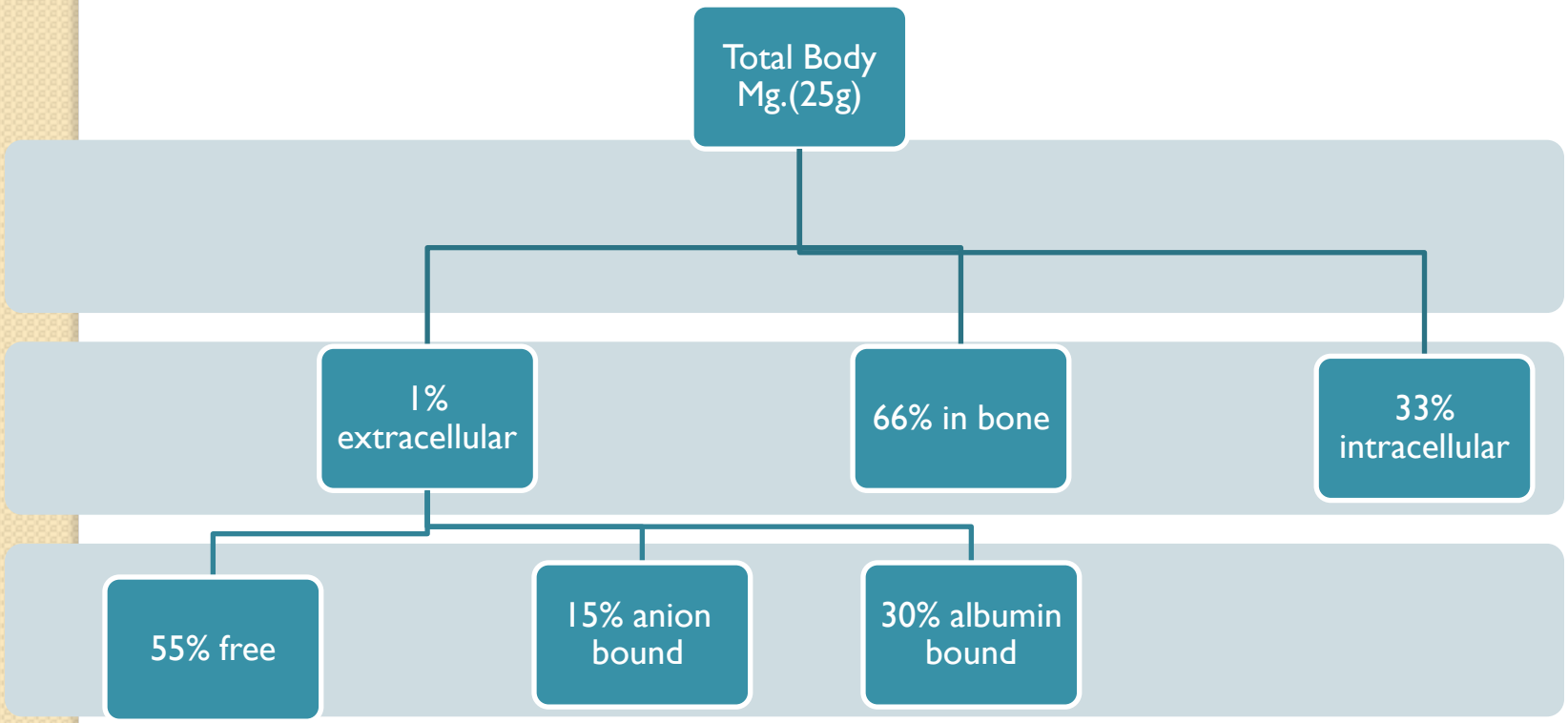
Magnesium in Chronic Kidney Disease: Challenges and Opportunities



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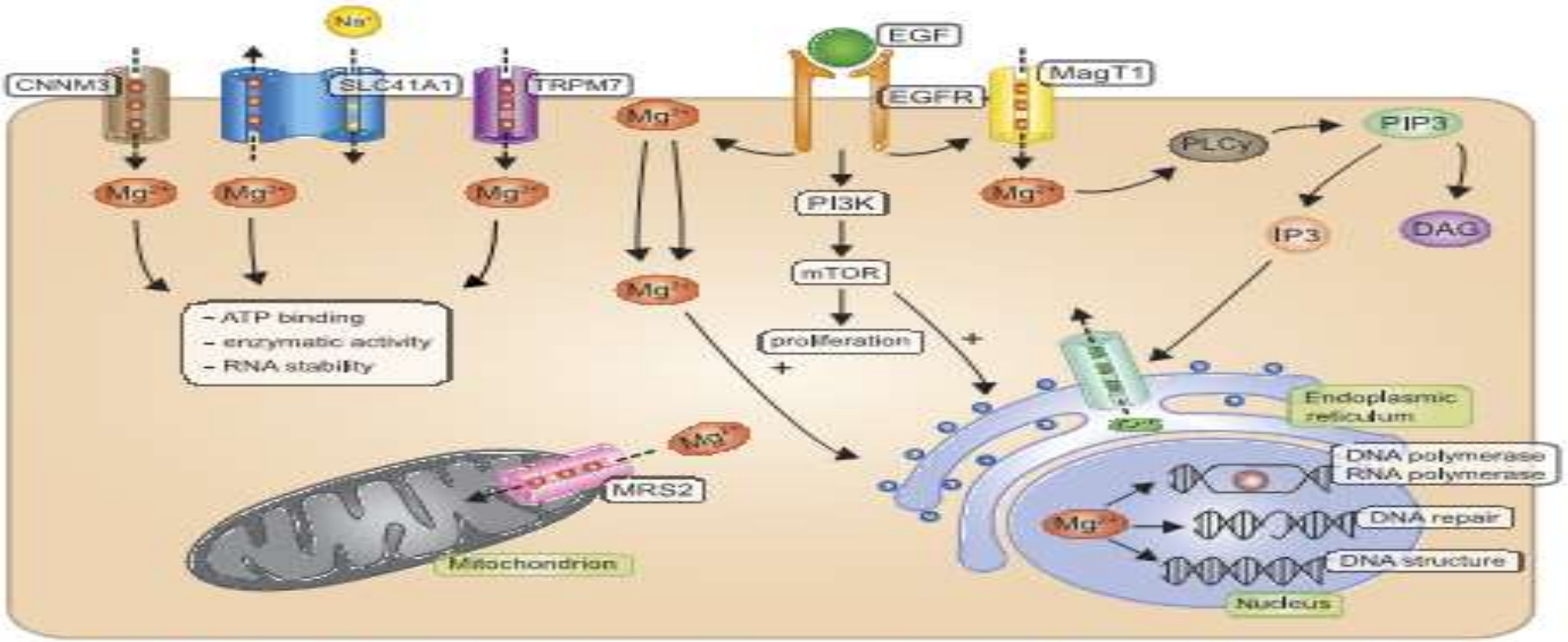

FIGURE 1. Magnesium in cellular physiology. Cellular Mg^{2+} homeostasis is regulated by the combined action of TRPM7, SLC41A1, MagT1, and CNNM3 Mg^{2+} transporters. MRS2 transporters regulate intramitochondriel Mg^{2+} concentrations. In the nucleus, Mg^{2+} is involved in DNA stability and DNA repair and regulates the activity of the DNA and RNA polymerases. Within the cell cytosol, Mg^{2+} regulates ATP binding, enzymatic activity of more then 600 enzymes, proliferation, and tRNA and mRNA stability. Activation of growth factor receptors, such as the EGFR, will increase Mg^{2+} uptake and release of membrane-bound Mg^{2+} resulting in mTOR activation and Ca^{2+} release from the ER. These mechanisms are essential for cell growth and proliferation. TRPM7, transient receptor potential melastatin type 7; CNNM3, cyclin M3; SLC41A1, solute carrier family 41 type 1; MagT1, magnesium transporter 1; MRS2, mitochondrial RNA splicing 2; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; PI3K, phosphoinositide 3-kinase; mTOR, mammalian target of rapamycin; PLCγ, phospholipase C-γ; PIP_3, phosphatidylinositol 3,4,5-triesphosphate; IP_3, inositol trisphosphate.

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Name	Membrane	Expression	Permeability	Mechanism	Disease	Reference Nos.
			General Mg^{2+} transporters			
TRPM7	Plasma membrane	Ubiquitous	Ba>Ni>Mg>Ca	Channel		314, 349
MagT1	Plasma membrane	Ubiquitous	Mg>Ba>Fe=Cu	Channel	X-MEN syndrome	187, 311
SLC41A1	Plasma membrane	Ubiquitous	Mg>Sr>Fe>Ba>Cu	Exchanger	Nephronophthisis-like	185, 251, 289
SLC41A2	Golgi membrane	Ubiquitous	Mg>Ba>Ni>Ca	Exchanger		442
CNNM3	Plasma membrane	Ubiquitous	Mg>Fe>Cu>Co	Transporter?		545
MRS2	Mitochondrial membrane	Ubiquitous	Mg>Ni	Channel		388
			Tissue-specific Mg^{2+} transporters			
TRPM6	Apical plasma membrane	Kidney, intestine	Ba>Ni>Mg>Ca	Channel	Hypomagnesemia secondary hypocalcemia	314
CNNM1	?	Brain	Cu>Mg?	?		13, 545
CNNM2	Basolateral plasma membrane	Kidney	Mg>Sr>Zn>Cd	Transporter? Sensor?	Hypomagnesemia with seizures and mental retardation	184, 497
CNNM4	Basolateral plasma membrane	Intestine	Mg	Exchanger?	Jalili syndrome	387, 402, 575

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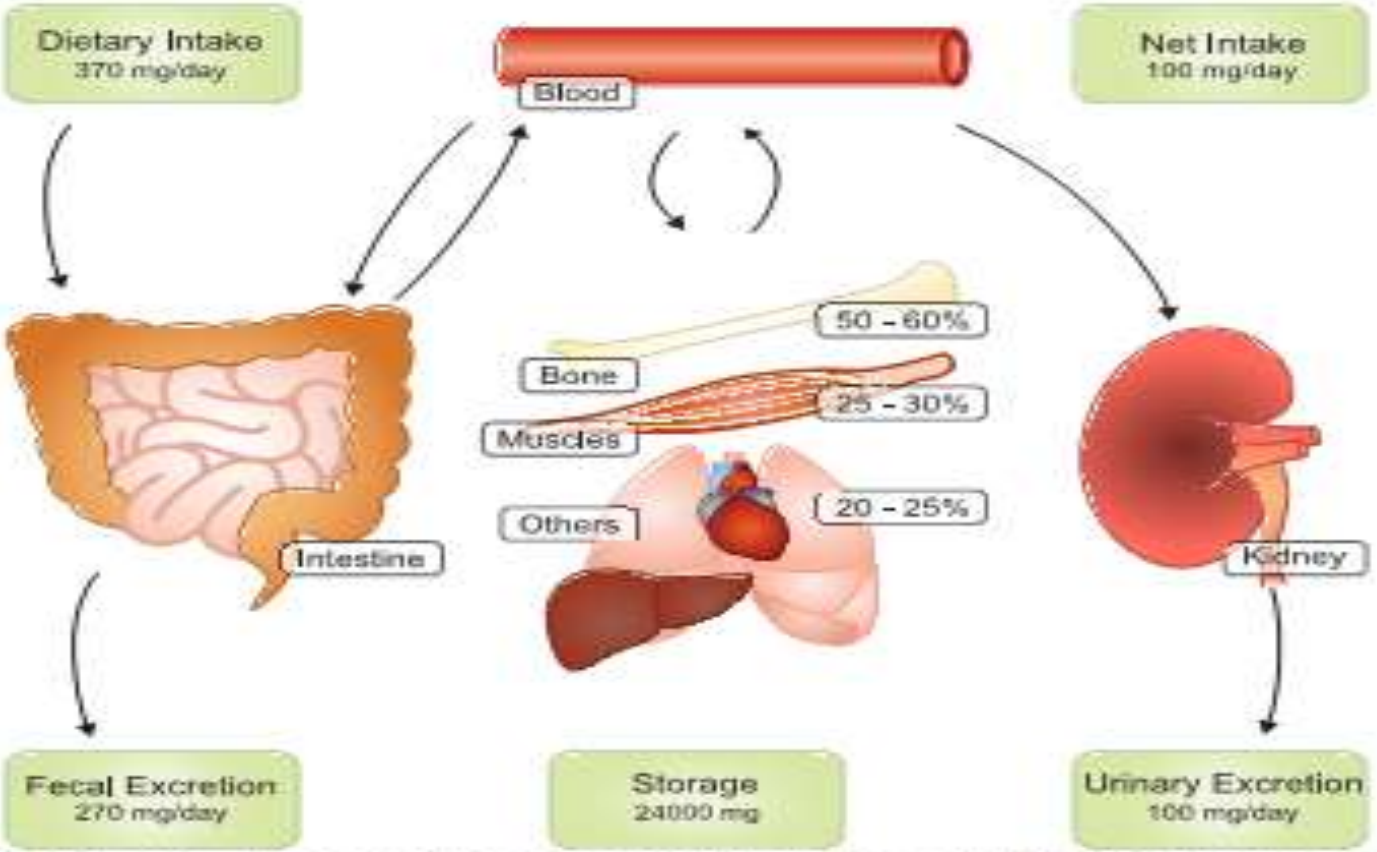

FIGURE 2. Magnesium homeostasis. Panels represent the daily amount of Mg^{2+} intake and excretion. Daily the intestines absorb ~120 mg and secrete 20 mg of Mg^{2+}, resulting in a net absorption of 100 mg. In the kidney daily ~2,400 mg Mg^{2+} is filtered by the glomerulus, of which 2,300 mg is reabsorbed along the kidney tubule. This results in a net excretion of 100 mg, which matches the intestinal absorption. Bone and muscle provide the most important Mg^{2+} stores.

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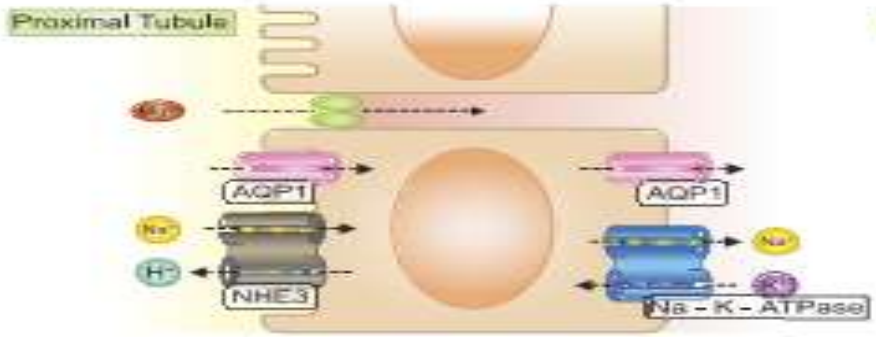

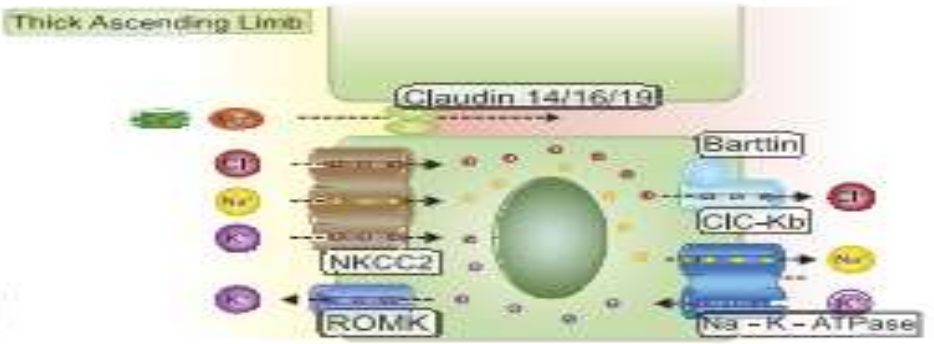

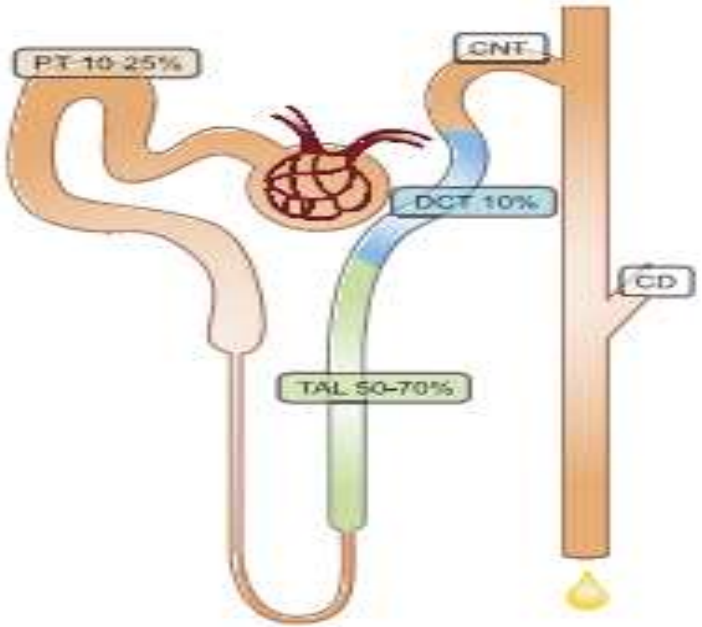

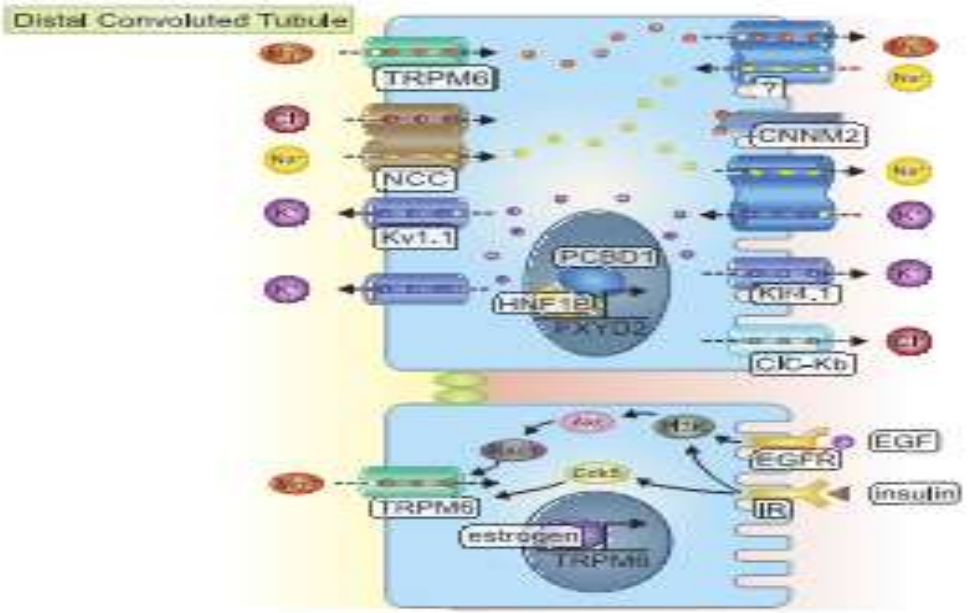

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Table 4. *Drug-induced Mg^{2+} disturbances*

Class	Drug	Mechanism	Prevention/Treatment	Reference Nos.
		Drug-induced hypomagnesemia		
Diuretics	Furosemide	TAL: reduced paracellular Mg^{2+} reabsorption	Combined K^+ and Mg^{2+} supplementation, Switch to K^+ and Mg^{2+}-sparing diuretics such as amyloride	92, 101, 127, 368
	Thiazide	DCT: reduced TRPM6 expression		
EGFR inhibitors	Cetuximab	DCT: reduced TRPM6 activity	Mg^{2+} supplementation Cetuximab users may switch to erlotinib	341, 459, 510
Proton pump inhibitors	Omeprazole, lansoprazole, pantoprazole, rabeprazole, etc.	Intestine: reduced Mg^{2+} absorption	Mg^{2+} supplementation Switch to histamine2 receptor antagonists	144, 226
Calcineurin inhibitors	Cyclosporin A, tacrolimus	DCT: reduced TRPM6 expression	Mg^{2+} supplementation	39, 517
Platinum derivates	Cisplatin, carboplatinum	DCT: cell death? Reduced TRPM6 expression?	Mg^{2+} supplementation	142, 453, 495, 583
Antimicrobials	AGAs	TAL: reduced paracellular Mg^{2+} reabsorption	Mg^{2+} supplementation	23, 38, 169, 188, 535, 562, 585
	Pentamidine	DCT: cell death?		
	Rapamycin	TAL: reduced paracellular Mg^{2+} reabsorption		
	Amphotericin B	?		
	Foscaret	Mg^{2+} chelating		
		Drug-induced hypermagnesemia		
Epsom salt poisoning	$MgSO_4$	Intestinal Mg^{2+} overload	Hemodialysis	52, 231
Cathartics	$Mg_3(C_6H_5O_7)_2$	Intestinal Mg^{2+} overload	Switch to polyethyleneglycol or electrolyte lavage solutions	378, 451
Laxatives	$MgSO_4$, $Mg[OH]_2$, $Mg_3(C_6H_5O_7)_2$	Intestinal Mg^{2+} overload	Switch to bulk [fiber-based] laxatives	413, 521, 586
Enema	$MgSO_4$	Intestinal Mg^{2+} overload	Switch to fleet [sodium phosphate] enema	

EGFR, epidermal growth factor receptor; TAL, thick ascending limb of Henle's loop; DCT, distal convoluted tubule; TRPM6, transient receptor potential melastatin type 6; AGAs, aminoglycoside antibiotics.

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Table 2. *Therapeutic use of Mg^{2+}*

Disease	Cochrane Review	Large-Scale Clinical Studies
	First drug of choice	
Preeclampsia	RR: 0.41, 95% CI: 0.29–0.58 [130]	
Arrhythmia–Torsades des Pointes		
	Alternative drug of choice	
Migraine		
Asthma	RR: 0.53, 95% CI: 0.05–5.31 [404]	Magnetic
Super-refractory status epilepticus		
Muscle cramps	No. cramps: −3.93%, 95% CI: −21.12 to 13.26% [168]	
	Experimental	
Stroke		FAST-MAG Imagea
Subarachnoid hemorrhage	RR: 0.75, 95% CI: 0.57–1.00* [125]	IMASH MASH-II
Myocardial infarction	OR: 0.58, 95% CI: 0.49–0.70* [312]	LIMIT-2 ISIS-4
Hypertension	DBP: −2.2 mmHg, 95% CI: −3.4 to −0.9 [118]	
Traumatic brain injury	GS: 0.02, 95% CI: −0.38 to 0.041 [25]	

MAGNESIUM AND CKD

Regression of vascular calcification in chronic kidney disease – feasible or fantasy? A review of the clinical evidence

Oscar Leonard,[1] Jonas Spaak[2] & David Goldsmith[1]

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J Bras Nefrol 2013;35(2):147-161

Vascular calcification in chronic kidney disease: a review

TABLE 1 SUMMARY OF THE MOST COMMON INHIBITORY AND STIMULATORY FACTORS INVOLVED IN THE PATHOGENESIS OF VASCULAR CALCIFICATION

Inhibitors	Promoters
Matrix Gla protein (MGP)	Hyperphosphatemia
Osteopontin (OPN)	Hypercalcemia
Bone morphogenic protein 7 (BMP-7)	Bone morphogenic protein 2 (BMP-2)
Magnesium	Receptor activator of nuclear factor-*kappa* B ligand (RANKL)
Fetuin-A	
Osteoprotegerin (OPG)	
Pyrophosphate (PPi)	
Klotho	
FGF-23 (?)	FGF-23 (?)

TRENDS IN CARDIOVASCULAR MEDICINE ▮ (2014) ▮▮▮–▮▮▮

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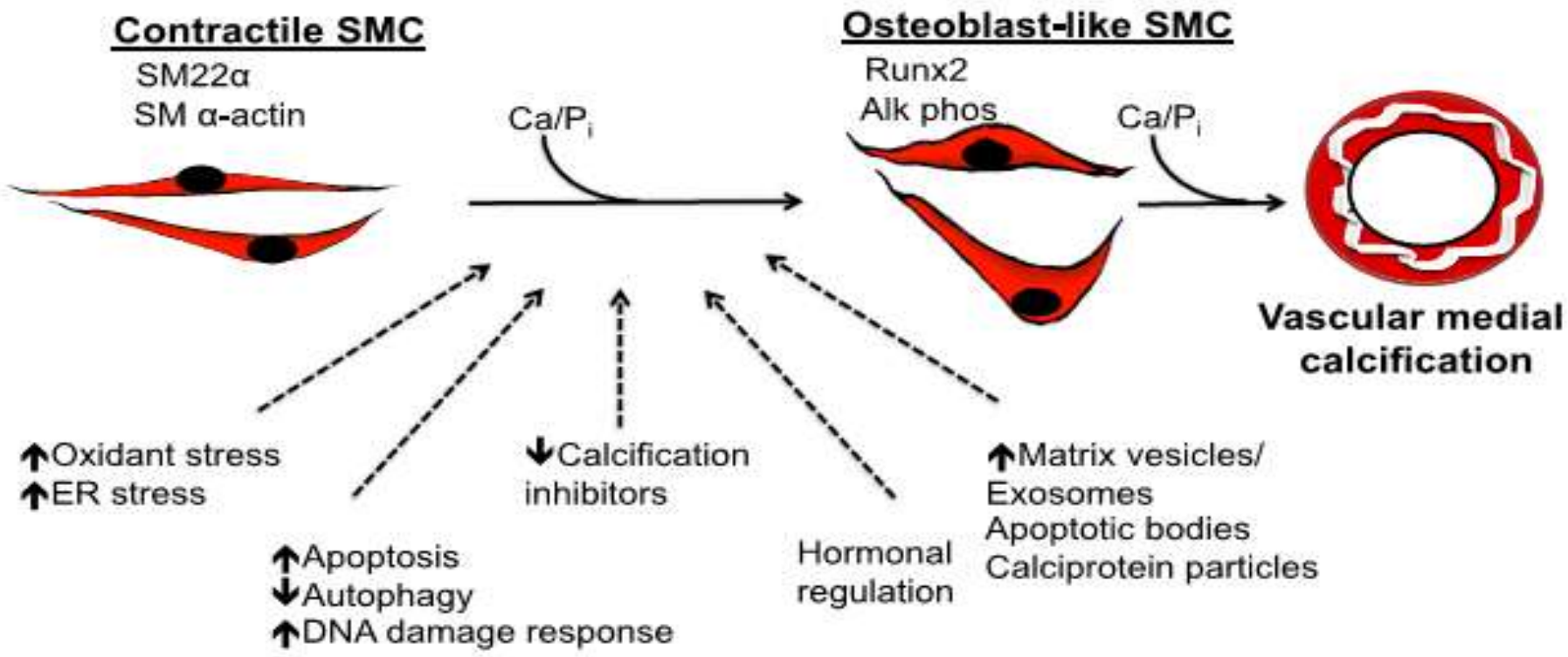
Vascular calcification: Mechanisms of vascular smooth muscle cell calcification

*Jane A. Leopold**



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Vascular calcification: Mechanisms of vascular smooth muscle cell calcification

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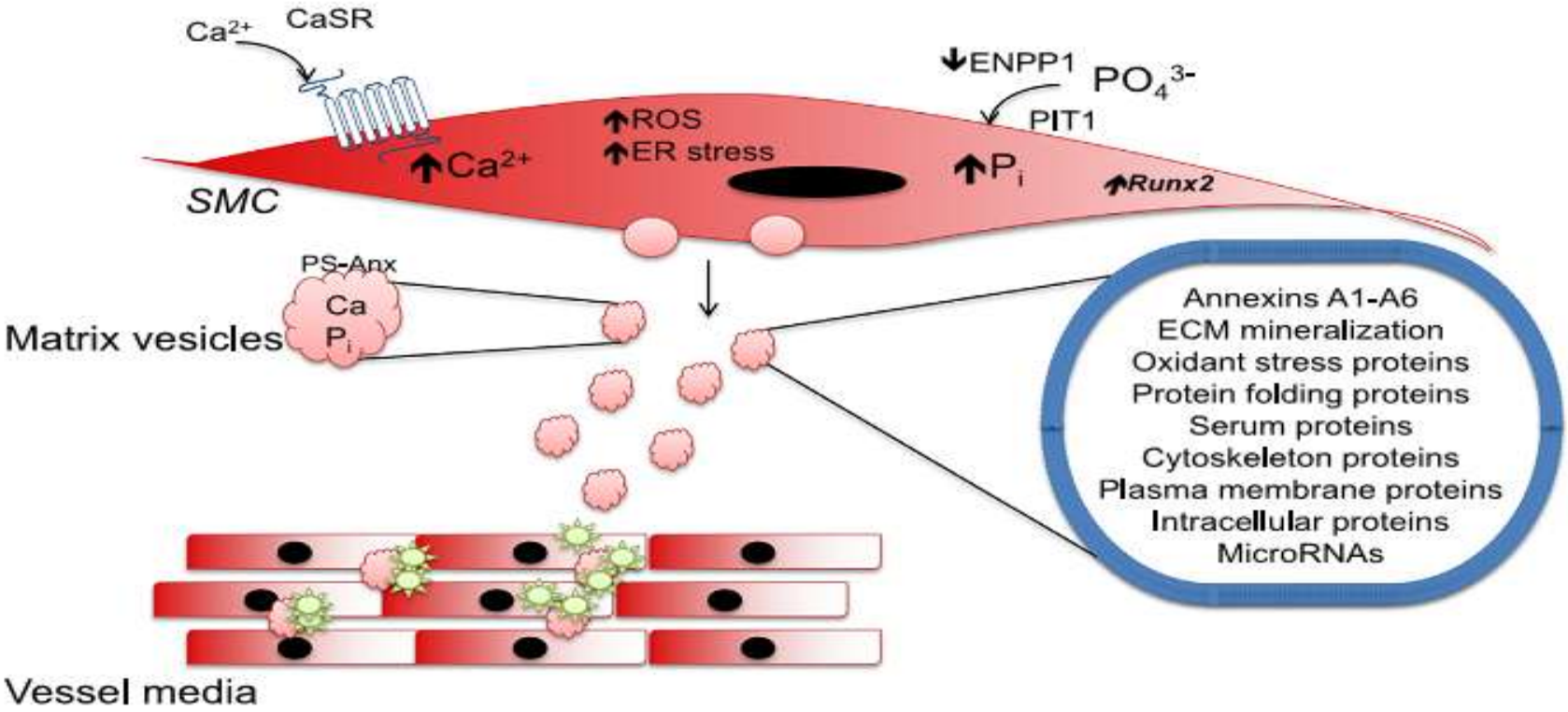

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Magnesium in Chronic Kidney Disease: Challenges and Opportunities

Mg Balance in ESRD Patients

Renal failure is the most common cause of hypermagnesemia, which is usually mild and asymptomatic even in ESRD patients. In CKD, until GFR falls to below 30 ml/min, urinary Mg excretion may be normal or even increased. As CKD progresses (<30 ml/min), urinary Mg excretion may be insufficient to balance intestinal Mg absorption, at which point dietary Mg intake then becomes a major determinant of serum and total body Mg levels [16]. However, administration of Mg-containing drugs (e.g. antacids and laxatives) and high Mg concentrations of dialysate may provoke severe, symptomatic or even fatal hypermagnesemia [12]. On the other hand, many fac-

tients, and some conditions lead to a negative Mg balance in these patients, such as excessive intake of diuretics, reduced gastrointestinal uptake (due to acidosis, and poor nutrition and absorption) and a low Mg concentration of dialysate [17]. In patients with CKD on dialysis, bone Mg

Schmulen et al. [19] demonstrated that Mg absorption in the human jejunum is dependent on vitamin D, and they showed that 1-α,25-dihydroxyvitamin D_3 therapy in patients with CKD is associated with an enhanced jejunal absorption of Mg.

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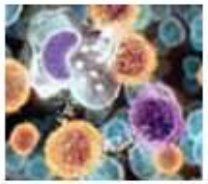
In ESRD,
- Controls serum phosphate
- Controls hyperparathyroidism

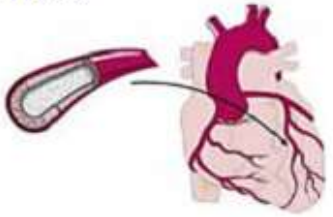
- ↓ Serum PTH level

In ESRD,
- ↓ Vascular calcification
- ↓ Left ventricular hypertrophy
- ↓ Mortality



Mg

- Suppresses inflammation
- ↓ Immune response
- ↑ Specific immune response
- ↓ Constitutive nitric oxide synthase



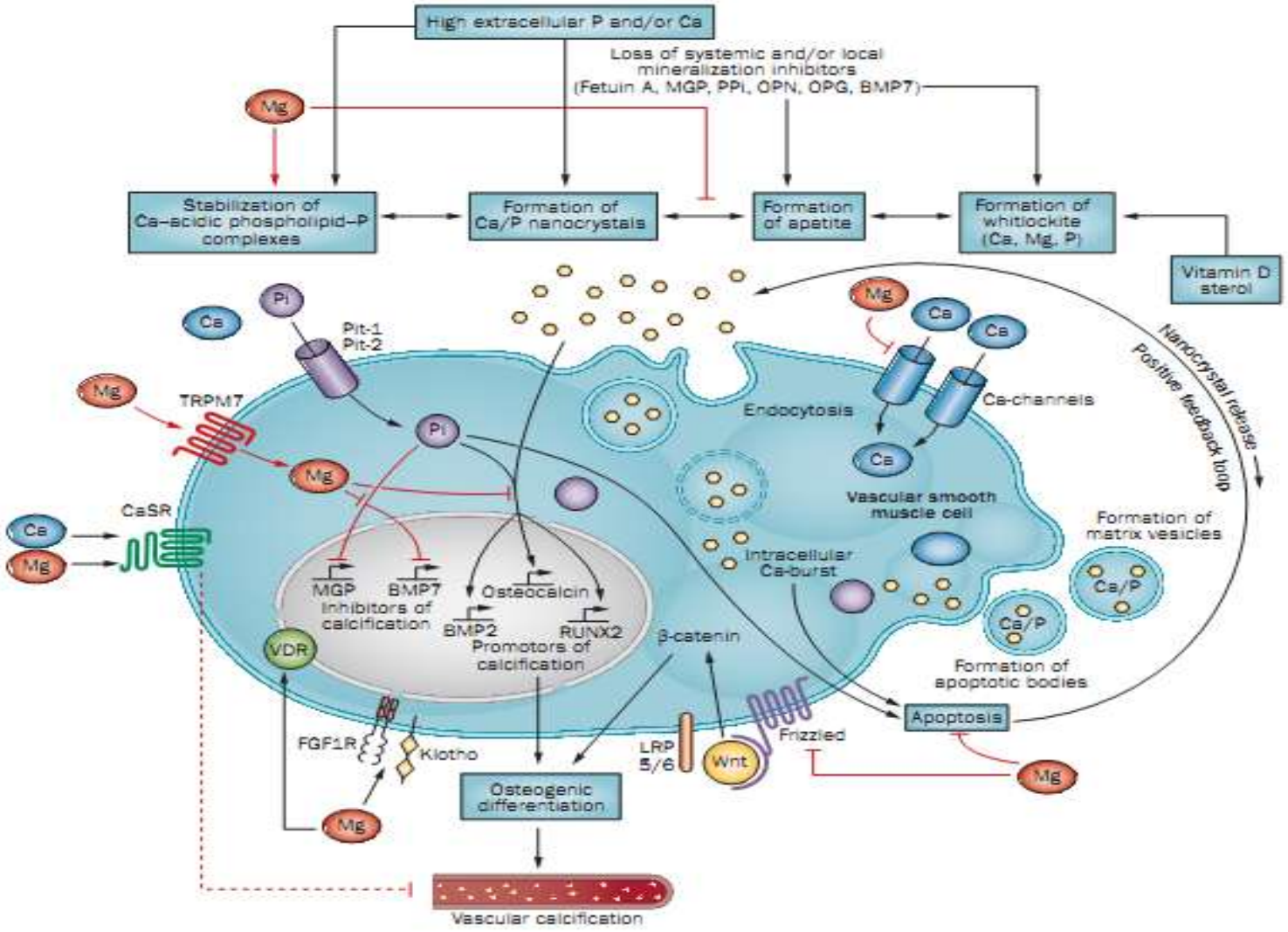
-Regulates vascular tone
-Regulates heart rhythm
-Regulates blood pressure
-Prevents thrombosis
-Prevents atherosclerosis

- Prevents insulin resistance
- Prevents arrhythmias
- Prevents osteoporosis

Magnesium and cardiovascular complications of chronic kidney disease

Ziad A. Massy and Tilman B. Drüeke

Nat. Rev. Nephrol. advance online publication 12 May 2015



JACC Cardiovasc Imaging. 2014 January ; 7(1): 59–69. doi:10.1016/j.jcmg.2013.10.006.

Magnesium Intake Is Inversely Associated With Coronary Artery Calcification:

The Framingham Heart Study

We observed strong, favorable associations between higher self-reported total (dietary and supplemental) magnesium intake and lower calcification of the coronary arteries, an

American Journal of Nephrology

Am J Nephrol 2012;35:31–39
DOI: 10.1159/000334742

Relationship between Magnesium and Clinical Biomarkers on Inhibition of Vascular Calcification

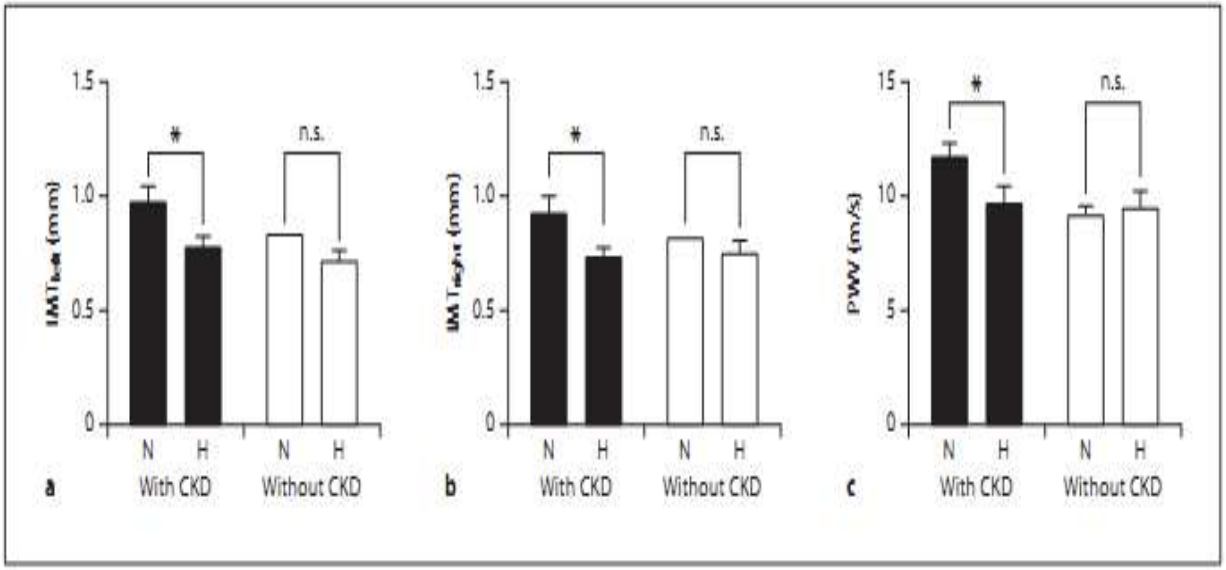


Fig. 3. a IMT of the left common carotid artery classified by Mg^{2+} serum concentration in patients with CKD (filled bar; normal vs. high Mg^{2+} range) and in controls without CKD (open bar; normal vs. high Mg^{2+} range). **b** IMT of the right common carotid artery classified by Mg^{2+} blood serum concentration in patients with CKD (filled bar; normal vs. high Mg^{2+} range) and in controls without CKD (open bar; normal vs. high Mg^{2+} range). **c** PWV associated by Mg^{2+} blood serum concentration in patients with CKD (filled bar; normal vs. high Mg^{2+} range) and in controls without CKD (open bar; normal vs. high Mg^{2+} range). N = Normal; H = high.

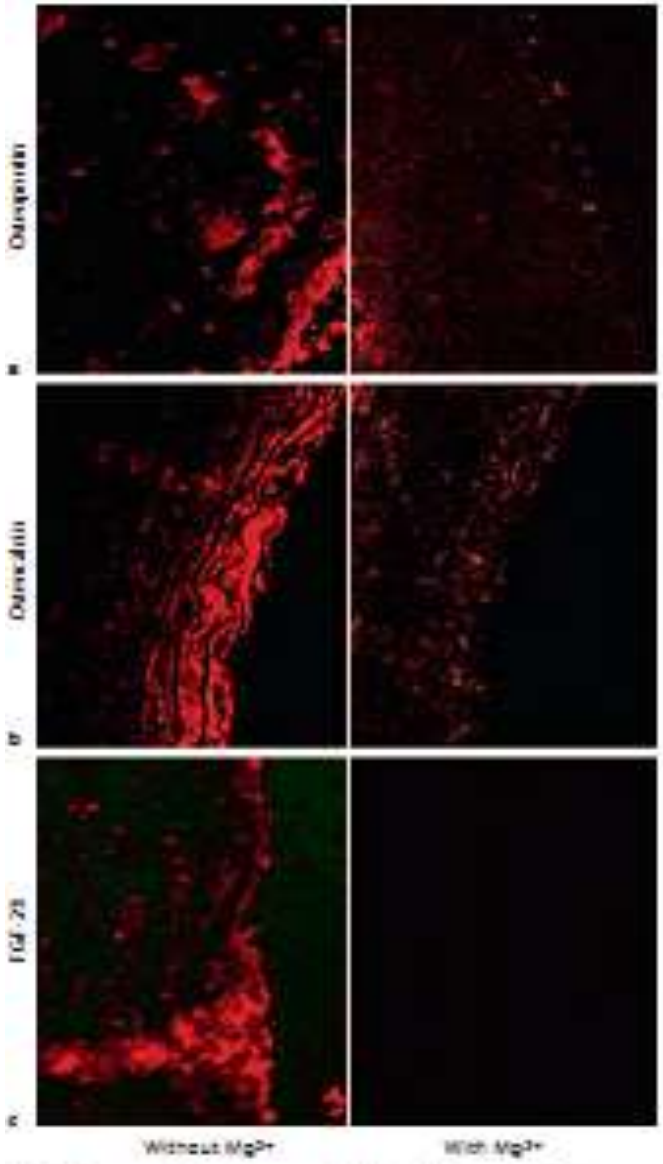


Fig. 2. Representative immunohistological images of aortic segments from male Wistar-Kyoto rats showing (a) osteopontin, (b) osteocalcin, and (c) FGF-23 staining after incubation in the absence (left image) and presence (right image) of Mg^{2+} in the incubation media.

Posadas-Sánchez et al. Nutrition Journal (2016) 15:22
DOI 10.1186/s12937-016-0143-3

Nutrition Journal

RESEARCH Open Access

Serum magnesium is inversely associated with coronary artery calcification in the Genetics of Atherosclerotic Disease (GEA) study

Objective: The aim of this study was to examine the cross-sectional association of serum magnesium levels with CAC.

Methods: We included 1276 Mexican-mestizo subjects (50 % women), aged 30–75 years, free of symptomatic cardiovascular disease. CAC was quantified by multidetector computed tomography using the method described by Agatston. Cross-sectional associations of serum magnesium with cardiometabolic factors and subclinical atherosclerosis defined as a CAC score > 0, were examined in logistic regression models adjusted for age, sex, education, smoking status, body mass index, systolic blood pressure, physical activity, elevated abdominal visceral tissue, fasting insulin and glucose, alcohol consumption, menopausal status (women only), low (LDL-C) and high density lipoprotein cholesterol (HDL-C), triglycerides, diuretic use, type 2 diabetes mellitus (DM2), and family history of DM2.

Results: After full adjustment, subjects in the highest quartile of serum magnesium had 48 % lower odds of hypertension ($p = 0.028$), 69 % lower odds of DM2 ($p = 0.003$), and 42 % lower odds of CAC score > 0 ($p = 0.016$) compared to those with the lowest serum magnesium. The analyses also showed that a 0.17 mg/dL (1SD) increment in serum magnesium was independently associated with 16 % lower CAC (OR 0.84, 95 % CI 0.724–0.986).

Conclusions: In a sample of Mexican-mestizo subjects, low serum magnesium was independently associated to higher prevalence not only of hypertension and DM2, but also to coronary artery calcification, which is a marker of atherosclerosis and a predictor of cardiovascular morbidity and mortality.

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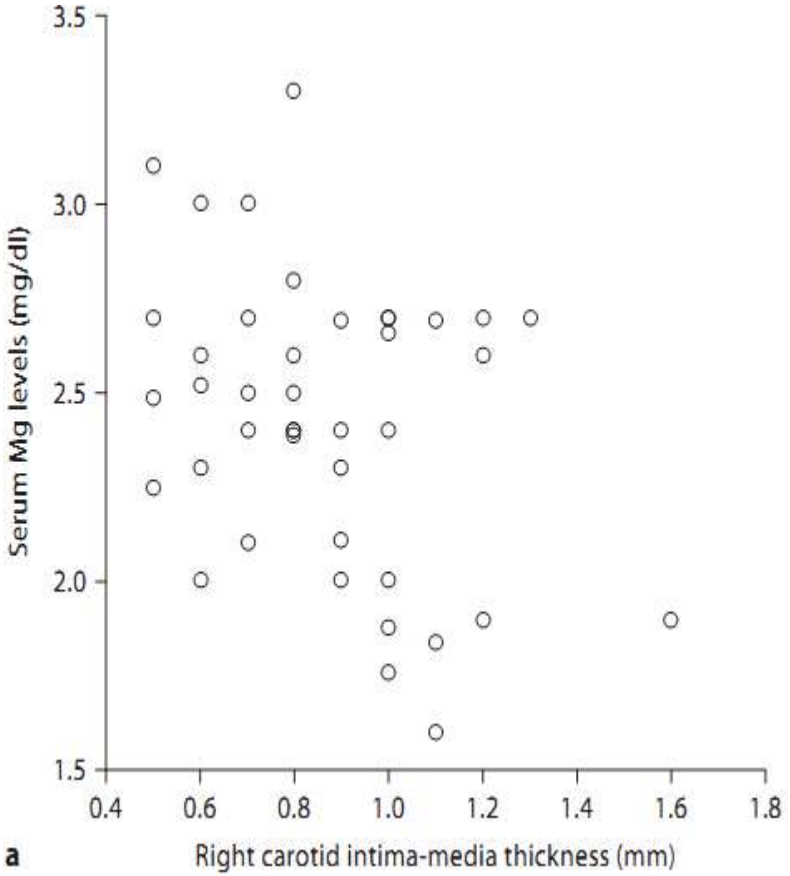
Magnesium in Chronic Kidney Disease: Challenges and Opportunities

spectively). Turgut et al. [8] also demonstrated an inverse association between serum Mg and carotid intima-media thickness in HD patients (fig. 2). They found that, while the mean serum calcium and phosphorus did not change significantly, carotid intima-media thickness and PTH improved significantly after Mg supplementation within 2 months. The authors suggested that the beneficial effect of Mg on carotid intima-media thickness might be due to the decreased serum PTH level. Furthermore, Mg-con-



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Research Article

Low Magnesium Levels and FGF-23 Dysregulation Predict Mitral Valve Calcification as well as Intima Media Thickness in Predialysis Diabetic Patients

factor-23 (FGF-23) levels with mitral valve calcification and IMT in CKD diabetic patients. *Methods*. Observational, prospective study involving 150 diabetic patients with mild to moderate CKD, divided according to Wilkins Score. Carotid-echodoppler and

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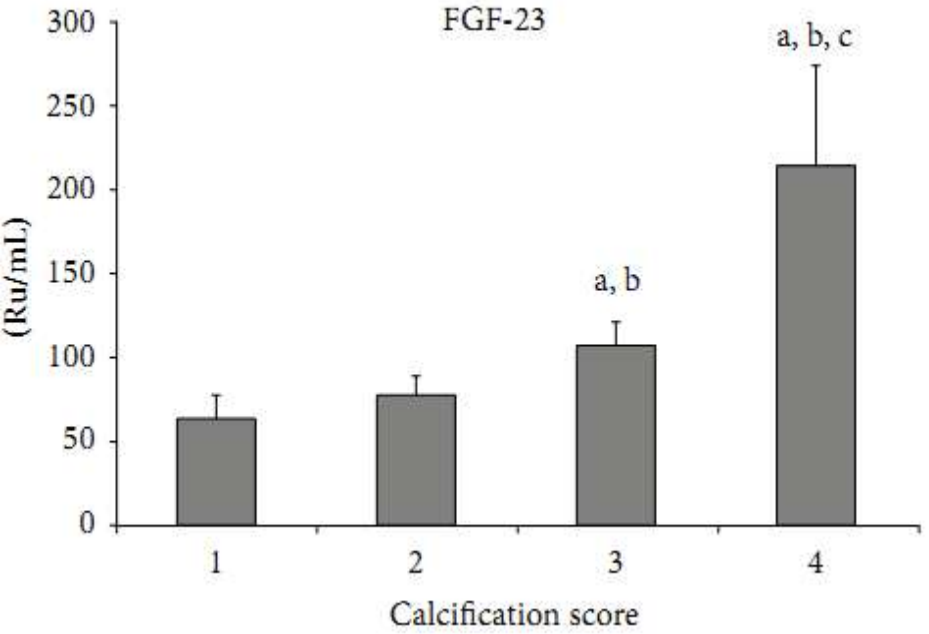

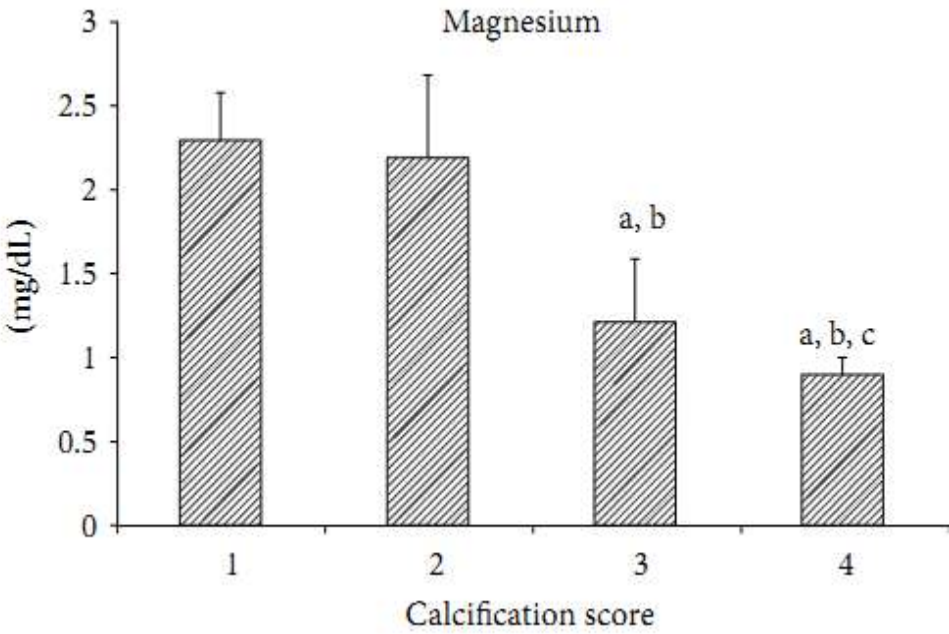

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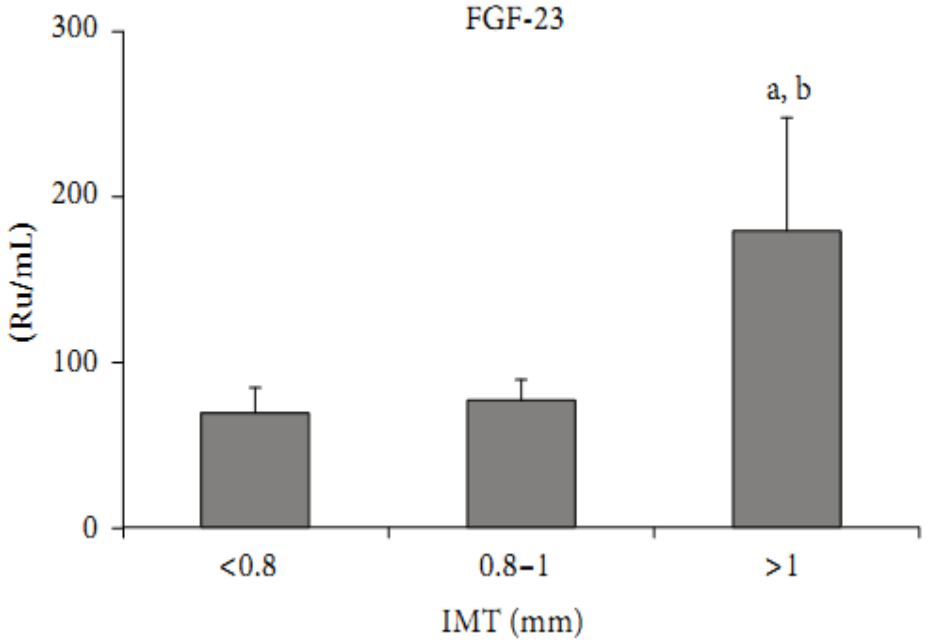

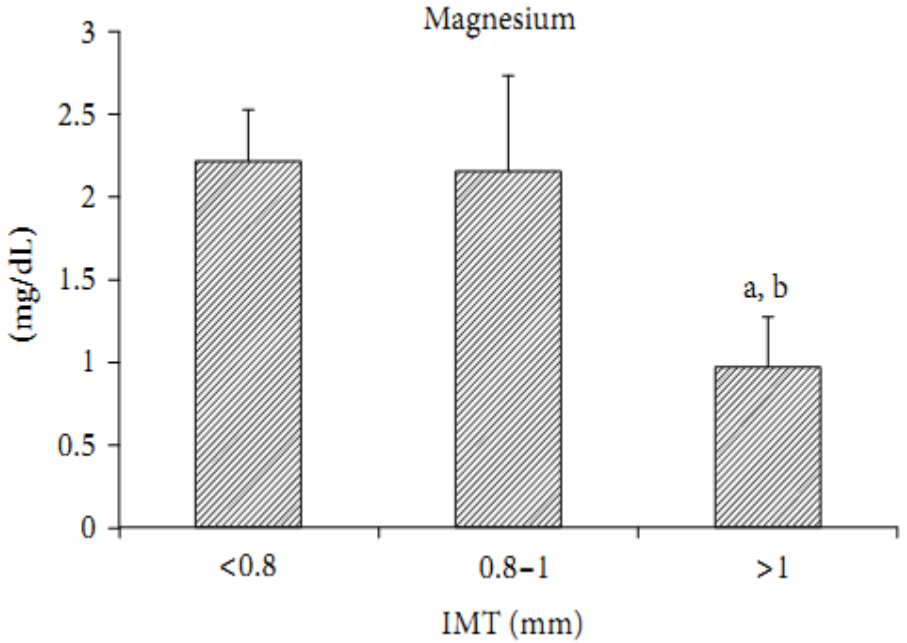

Magnesium Modifies the Impact of Calcitriol Treatment on Vascular Calcification in Experimental Chronic Kidney Disease

J Pharmacol Exp Ther 355:451–462, December 2015

Chronic kidney disease (CKD) patients are commonly treated with vitamin D analogs, such as calcitriol. Recent epidemiologic evidence revealed a significant interaction between vitamin D and magnesium, since an inverse relationship between vitamin D levels and mortality mainly occurs in patients with a high magnesium intake. The aim of the study was to assess the mechanisms involved by determining whether magnesium alone or combined with calcitriol treatments differentially impacts vascular calcification (VC) in male Sprague-Dawley rats with adenine-induced CKD. Treatment with moderate doses of calcitriol (80 μg/kg) suppressed parathyroid hormone to near or slightly below control levels. Given alone, this dose of calcitriol increased the prevalence of VC; however, when magnesium was given in combination, the severity of calcification was attenuated in the abdominal aorta (51% reduction), iliac (44%), and carotid arteries (46%) compared with CKD controls. The decreases in vascular calcium content were associated with a 20–50% increase in vascular magnesium. Calcitriol treatment alone significantly decreased TRPM7 protein (↓ to ~11%), whereas the combination treatment increased both mRNA (1.7×) and protein (6.8×) expression compared with calcitriol alone. In summary, calcitriol increased VC in certain conditions, but magnesium prevented the reduction in TRPM7 and reduced the severity of VC, thereby increasing the bioavailable magnesium in the vascular microenvironment. These findings suggest that modifying the adverse effect profile of calcitriol with magnesium may be a plausible approach to benefiting the increasing number of CKD patients being prescribed calcitriol.

RESEARCH ARTICLE

Characterisation of Calcium Phosphate Crystals on Calcified Human Aortic Vascular Smooth Muscle Cells and Potential Role of Magnesium

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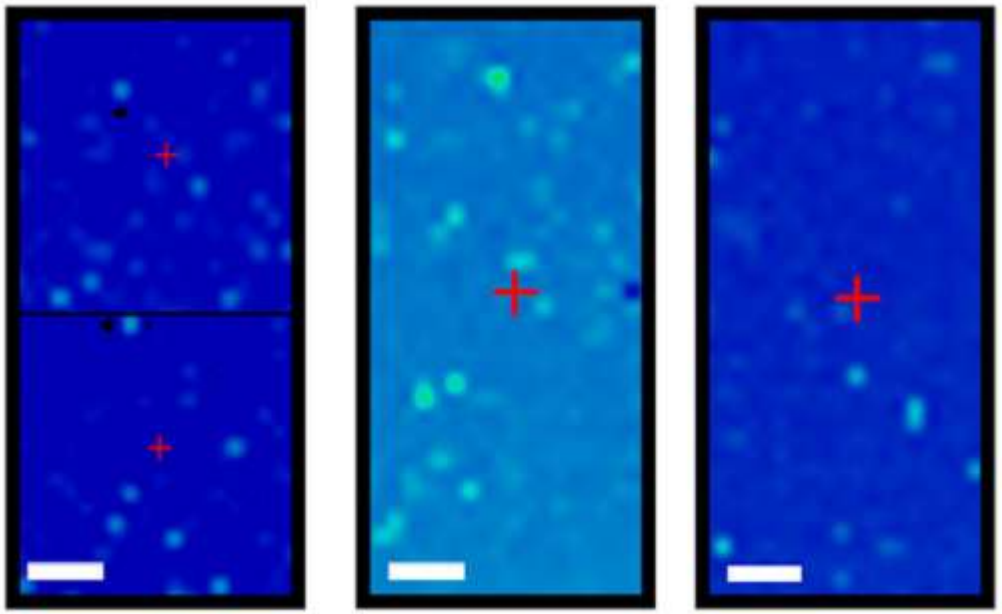

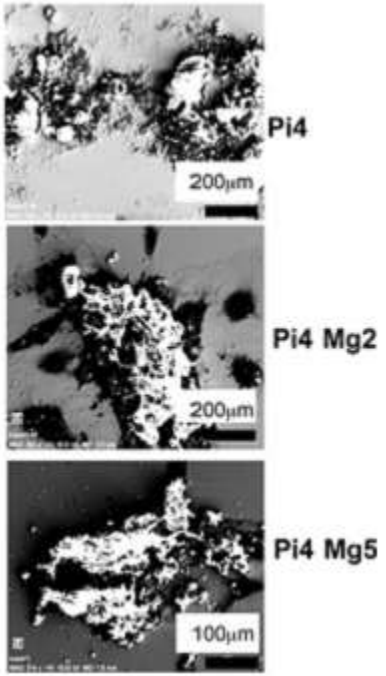

In summary, our data are excluding a physicochemical role of Mg^{2+} in inhibiting the crystal growth or in altering the calcium phosphate crystal composition or structure in an in vitro model of HAVSMC culture. Furthermore, the observed qualitative reduction of CPA spots should be linked to an active cellular role of Mg^{2+} in attenuating VC. Whether the in vitro data

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Magnesium and outcomes in patients with chronic kidney disease: focus on vascular calcification, atherosclerosis and survival

Table 1. Observational and interventional studies investigating the influence of serum magnesium levels on vascular calcification[a]

Authors (year)	Patients	Study design	Parameter	Assessment technique	P-value[b]
Observational studies					
Ishimura *et al.* (2007) [56]	390 (non-diabetic haemodialysis)	Prospective single blind follow-up over 4 months	Calcification of the hand arteries	Radiographic findings of the hands	0.036
Tzanakis *et al.* (2004) [62]	93 (haemodialysis) and 182 age- and sex-matched healthy controls	Cross-sectional analysis	Carotid intima–media thickness	B-mode ultrasound	0.001
Tzanakis *et al.* (1997) [60]	56 (haemodialysis)	Retrospective analysis of 8 years	Mitral annular calcification	Doppler echocardiography	0.008
Meema *et al.* (1987) [59]	44 (CAPD)	Prospective follow-up	Progression/regression of arterial calcification	Radiographic surveys	0.001
Interventional studies					
Spiegel *et al.* (2009) [71]	7 (haemodialysis)	Prospective interventional follow-up over 18 months (Mg carbonate)	CAC	Electron beam tomography	0.0737[c]
Turgut *et al.* (2008) [75]	47 (haemodialysis)	Prospective interventional follow-up over 2 months	Intima–media thickness of the carotid artery	Ultrasound	0.014[d]

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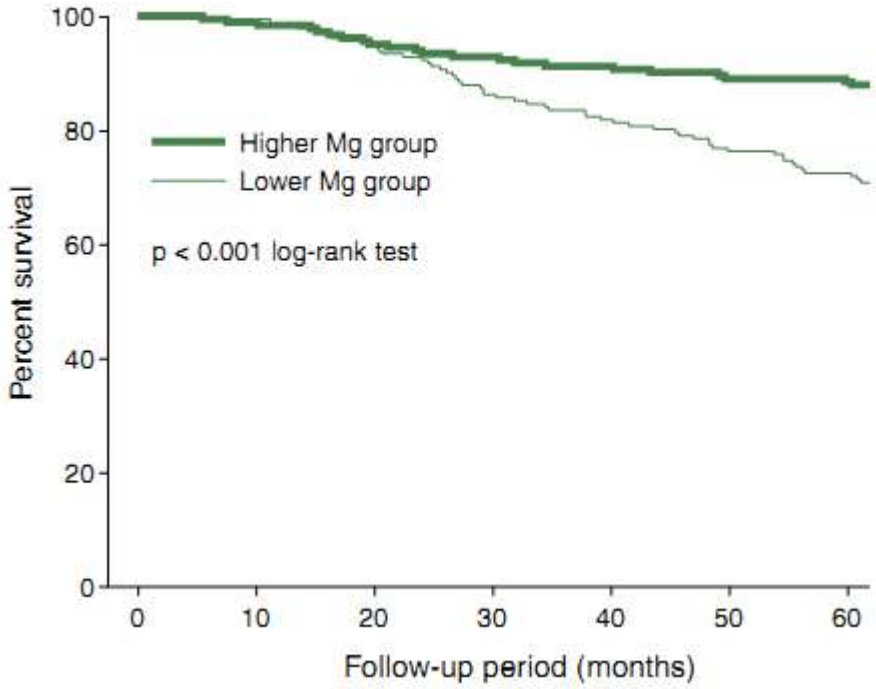

Blood Purification

Blood Purif 2010;29:280–292
DOI: 10.1159/000276665

Magnesium in Chronic Kidney Disease: Challenges and Opportunities

Other Relevant Cardiovascular Effects of Mg

correlated with intradialytic hypotension in HD. Hypomagnesemia has been shown to contribute significantly to cardiac morbidity and mortality, particularly in states associated with myocardial ischemia [90]. Mg therapy, both for deficiency replacement and in higher pharmacologic doses, has been beneficial in improving cardiovascular hemodynamics and electrophysiologic functioning. In a study by Kyriazis et al. [91], a dialysis solution containing 0.25 mmol/l Mg and 1.25 mmol/l Ca was identified as a major cause of intradialytic hypotension due to an impairment of myocardial contractility. They showed that increasing the dialysate Mg level to 0.75 mmol/l could prevent the intradialytic hypotension fre-

[91]. Mg deficiency-induced coronary vasospasm [92], defective energy metabolism [93] and excessive free radical generation [94] may be important variables acting in concert, or independently, to affect myocardial function. Plasma-ionized Mg also showed a negative correlation with QT dispersion, suggesting that Mg plays a role in maintaining myocardial electrical stability in HD patients.

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The Effect of Mg on Survival in ESRD Patients

There are only 2 studies which have tried to investigate the relationship between Mg and ESRD patient survival [87, 88]. Tzanakis et al. [87] found that lymphocyte Mg is an independent prognostic factor for improved survival ($p = 0.029$), while serum Mg had a similar but weaker relation ($p = 0.069$). Similarly, Ishimura et al. [88] investigated the prognostic value of serum Mg concentration for mortality in 515 patients on maintenance HD for a median follow-up time of 51 ± 17 months. They demonstrated that a lower serum Mg level was a significant predictor for mortality in HD patients, particularly for non-cardiovascular mortality [HR (per 1 mg/dl increase), 0.485 (95% CI: 0.241–0.975), $p = 0.0424$].

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Table 3. Summary of clinical trials involving magnesium-containing phosphate binders in patients undergoing dialysis[a]

Year	Author	Journal	Product	Modality	Patients (*N*)	Design/duration	Dialysate	Result
1982	Guillot *et al.* [6]	Nephron	$Mg(OH)_2$ and $Al(OH)_3$—separately and in combination	HD	9	Four open study phases: no phosphate binders (period I: 2 weeks), $Mg(OH)_2$ alone (II: 2–5 weeks), $Al(OH)_3$ plus $Mg(OH)_2$ (III: 4–10 weeks), $Al(OH)_3$ alone (IV: 4 weeks)	Mg, 0.5–0.75 mmol/L (1.0–1.5 mEq/L) and Ca, 1.5–1.6 mmol/L (3.0–3.25 mEq/L)	Best control of serum P levels when $Al(OH)_3$ and $Mg(OH)_2$ were used together.
1987	Oe *et al.* [9]	Clin Nephrol	$Mg(OH)_2$ and $Al(OH)_3$—separately and in combination	HD	18	Open, sequential: $Al(OH)_3$ alone (period I: 6–9 months), $Mg(OH)_2$ alone (II: 2–6.5 months) then $Al(OH)_3$ plus $Mg(OH)_2$ (III: 4–13 months)	Period I: Mg, 0.75 mmol/L; Periods II and III: Mg, 0.00 mmol/L	Allowed reduced aluminum usage. PTH levels fell on $Mg(OH)_2$ treatment (both when used as monotherapy or in conjunction with $Al(OH)_3$).
1986	O'Donovan *et al.* [7]	Lancet	$MgCO_3$ versus $Al(OH)_3$	HD	50	Two-year open-label study: 28 pts (chronic hospital-based haemodialysis) given $MgCO_3$, 22 pts (home-based dialysis) given $Al(OH)_3$	$MgCO_3$ group: Mg < 0.2 mmol/L and Ca, 1.65 mmol/L; $Al(OH)_3$ group: Mg, 0.85 mmol/L and Ca, 1.65 mmol/L	$MgCO_3$ suitable for long-term control of serum phosphate levels when used alone, but difficult to compare groups owing to different dialysis regimens.
1988	Moriniere *et al.* [8]	Nephrol Dial Transplant	$Mg(OH)_2$ versus $Al(OH)_3$	HD	20	Sequential open-label study: 20 pts for 6 months; 12 pts for 20 months.	Control period (with $Al(OH)_3$): Mg, 0.75 mmol/L; during $Mg(OH)_2$ period: Mg, 0.375 mmol/L	Replaced $Al(OH)_3$ with $Mg(OH)_2$. Diarrhoea common.
						Bone histomorphometry performed		Reduced requirement for supplemental calcium during $Mg(OH)_2$ treatment. During $Mg(OH)_2$ treatment, serum PTH levels declined non-significantly; stable serum concentrations of P, Ca, Mg and alkaline phosphatase.
1993	Parsons *et al.* [13]	Nephron	$MgCO_3/CaCO_3$ versus $CaCO_3$ versus $Al(OH)_3$	CAPD	50	One-year, open-label, parallel-group study: $MgCO_3$ + $CaCO_3$ (Group I: $n = 32$); $CaCO_3$ alone (II: $n = 10$), $Al(OH)_3$ alone (III: $n = 8$)	All patients given $MgCO_3$ + $CaCO_3$ were given Mg-free dialysate (Ca, 1.65 mmol/L)	Serum P levels were controlled equally well in the $MgCO_3$ + $CaCO_3$ group as in the other groups, without evidence of increased Mg levels. No significant between-group difference in PTH.

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Year	Author	Journal	Product	Modality	Patients (*N*)	Design/duration	Dialysate	Result
2007	Spiegel *et al.* [15]	J Ren Nutr	$MgCO_3/CaCO_3$ versus CaAc	HD	30	Twelve-week, randomized open-label pilot study: $MgCO_3$ + $CaCO_3$ (Group I; $n = 20$); CaAc alone (Group II; $n = 10$)	For both groups: Mg, 0.375 mmol/L (0.75 meq/L) and Ca, 1.25 mmol/L (2.5 meq/L)	Both regimens were generally well tolerated and $MgCO_3/CaCO_3$ was at least as effective in control of serum P as CaAc alone, but required less elemental Ca ingestion.
2008	Tzanakis *et al.* [16]	Int Urol Nephrol	$MgCO_3$ versus $CaCO_3$	HD	46	Six-month, randomized open-label study: $MgCO_3$ (Group I; $n = 25$) $CaCO_3$ (Group II; $n = 21$)	$MgCO_3$ group: Mg, 0.3 mmol/L and Ca, 1.50 mmol/L; $CaCO_3$ group: Mg, 0.48 mmol/L and Ca, 1.50 mmol/L.	The Mg regimen showed equally effective control of serum P and Mg, but better control of serum Ca, than the Ca regimen. Good tolerability profile for Mg regimen: 2 of 25 (8%) withdrew because of diarrhoea or high Mg levels.
2009	Spiegel *et al.* [17]	Hemodial Int	$MgCO_3/CaCO_3$	HD	7	Eighteen-month open-label pilot study to monitor CAC and V-BMD	Composition of dialysate not mentioned	There was no significant progression of the CAC score and no significant change in V-BMD, and thus Mg may have a favourable effect on these parameters (though the size of the study precludes any firm conclusions).
2009	McIntyre *et al.* [19]	Clin J Am Soc Nephrol	Fe–Mg hydroxycarbonate	HD	63	Five-week, randomized, placebo-controlled, double-blind parallel-group study: placebo (Group I; $n = 21$); Fe–Mg hyroxycarbonate, 1 g tds (Group II; $n = 21$); Fe–Mg hyroxycarbonate, 2 g tds (Group III; $n = 21$)	Composition of dialysate not mentioned	Lower dose had an acceptable tolerability profile, but only about half of this group had acceptable serum phosphorous control (<1.78 mmol/L). Higher dose group had acceptable phosphate control, with 81% achieving levels < 1.78 mmol/L, but tolerability profile was poor (13 of 21 [61.9%] discontinued owing to adverse events). Serum Mg levels were significantly elevated in both Fe–Mg groups versus placebo.
2010	de Francisco *et al.* [20]	Nephrol Dial Transplant	$CaAc/MgCO_3$ versus sevelamer-HCl	HD/HDF	255	Twenty-four-week, randomized, controlled, parallel-group investigator-blinded multicentre study: $CaAc/MgCO_3$ (Group I; $n = 126$); sevelamer-HCl (Group II; $n = 129$)	For both groups: Mg, 0.5 mmol/L and Ca, 1.5 or 1.25 mmol/L (dependent on prior prescription)	$CaAc/MgCO_3$ was non-inferior to sevelamer, with both treatments significantly lowering serum P by 25 weeks of therapy. Both treatments were equally well tolerated, with minimal increases in serum Ca and Mg levels in the $CaAc/MgCO_3$ group.

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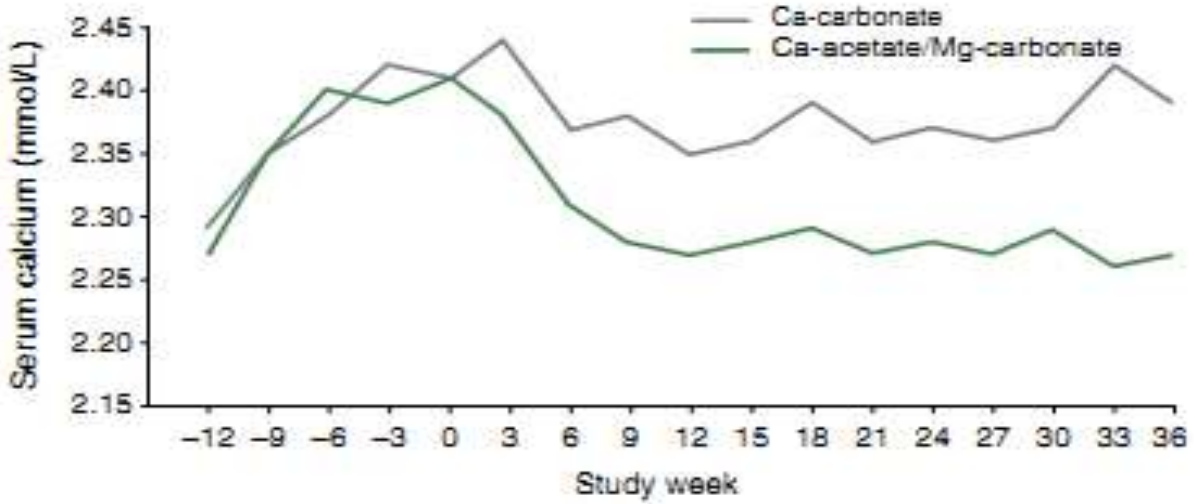

Combination treatment with magnesium carbonate and calcium acetate resulted in significantly lower serum phosphate and calcium concentrations compared with calcium carbonate monotherapy (both $P < 0.05$).

Blood Purification

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DOI: 10.1159/000321837

Magnesium in Chronic Kidney Disease: Unanswered Questions

ies are available. ***Conclusions:*** Magnesium balance remains poorly understood in patients with end-stage kidney disease. While observational and small randomized trials suggest that exogenous administration may be useful as a phosphate binder and may have protective cardiovascular effects in terms of both arrhythmias and vascular calcification, large randomized trials are needed to test these hypotheses.

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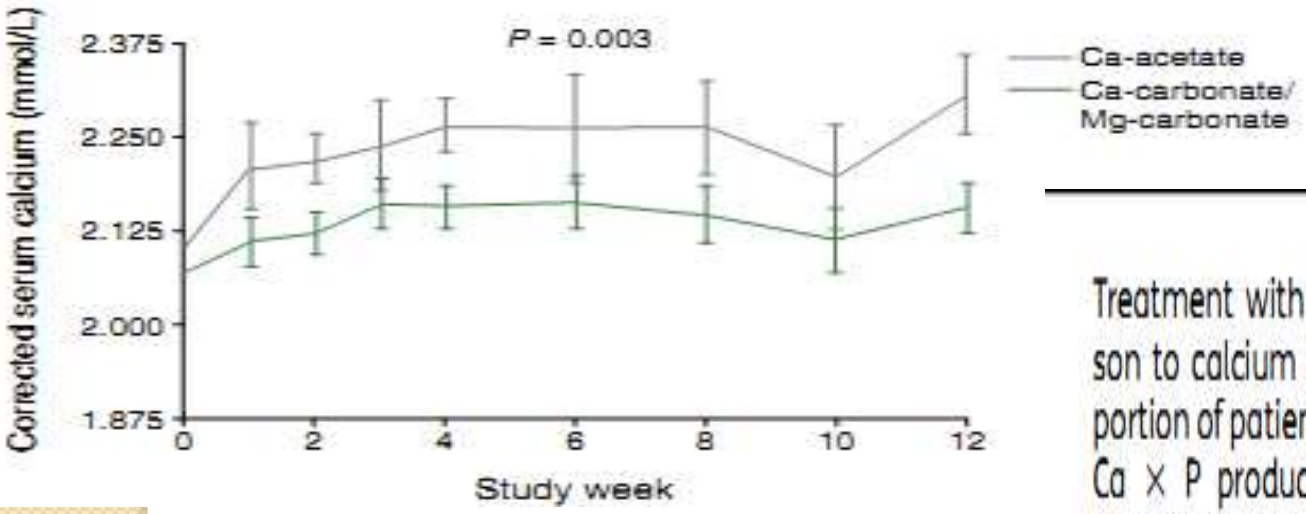

Treatment with magnesium carbonate in comparison to calcium carbonate resulted in a similar proportion of patients whose serum levels of phosphate, Ca × P product and iPTH fell within the K/DOQI guidelines, but more patients in the magnesium group than in the calcium group had serum calcium levels that fell within these guidelines ($P < 0.01$). Moreover, magnesium carbonate was generally well tolerated.

Combination therapy with magnesium carbonate and calcium carbonate offered control of serum phosphate that was at least as good as that with calcium acetate alone, but with significantly decreased elemental calcium consumption.

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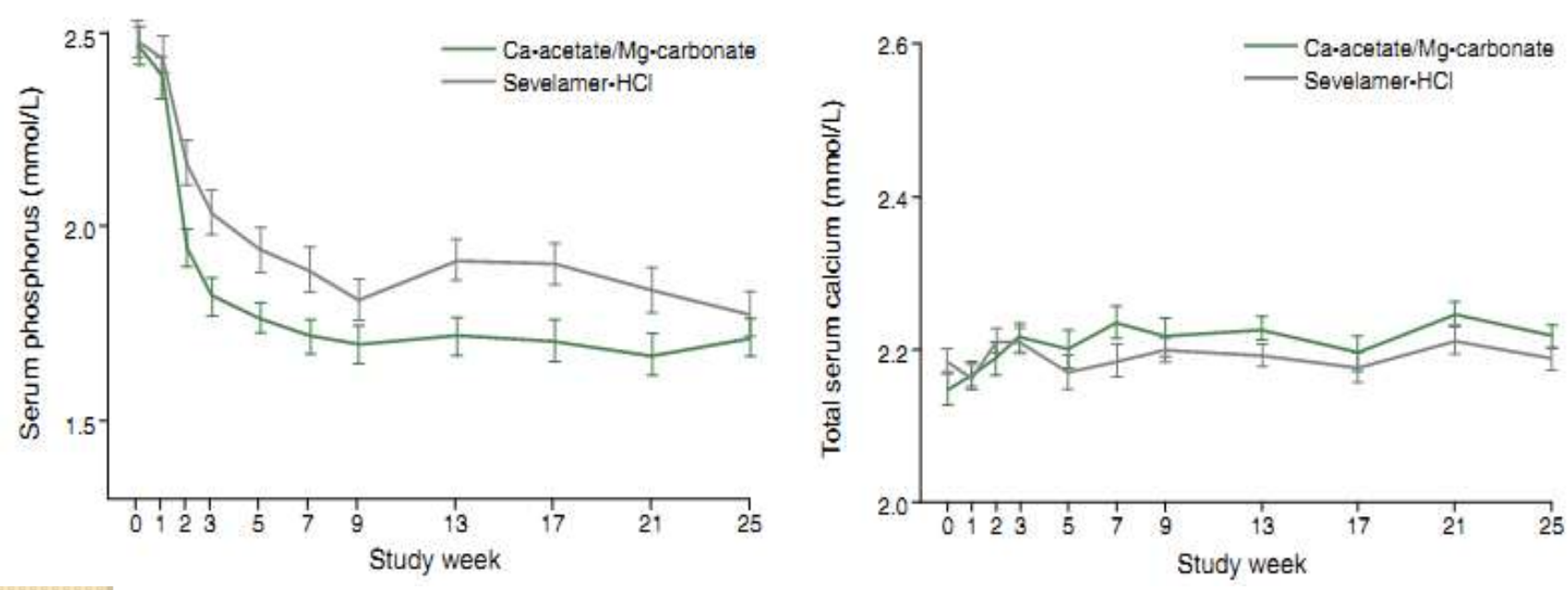

When used as a phosphate binder, the combination of calcium acetate/magnesium carbonate had a good tolerability profile and was non-inferior to sevelamer-HCl.

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